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Variant: NM_000152.4(GAA):c.2237G>A (p.Trp746Ter)

Version: 1.0

CA8815664

280063 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6b1d795d-e095-4a45-947e-c3f543da6b19
Approved on: 2020/5/5
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HGVS expressions

NM_000152.4(GAA):c.2237G>A (p.Trp746Ter)
NM_000152.4:c.2237G>A
NC_000017.11:g.80117015G>A
CM000679.2:g.80117015G>A
NC_000017.10:g.78090814G>A
CM000679.1:g.78090814G>A
NC_000017.9:g.75705409G>A
NG_009822.1:g.20460G>A
ENST00000570803.6:c.2237G>A
ENST00000572080.2:c.*375G>A
ENST00000577106.6:c.2237G>A
ENST00000302262.8:c.2237G>A
ENST00000302262.7:c.2237G>A
ENST00000390015.7:c.2237G>A
ENST00000572080.1:c.656G>A
ENST00000573556.1:n.190G>A
NM_000152.3:c.2237G>A
NM_001079803.1:c.2237G>A
NM_001079804.1:c.2237G>A
NM_001079803.2:c.2237G>A
NM_001079804.2:c.2237G>A
NM_000152.5:c.2237G>A
NM_001079803.3:c.2237G>A
NM_001079804.3:c.2237G>A

Pathogenic

Met criteria codes 4

PM2 PM3_Very Strong PVS1 PP4

Evidence Links 9

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.2237G>A (p.Trp746Ter), which results in a premature termination codon, is expected to result in nonsense mediated decay and absence of gene product, meeting PVS1. This is supported by the finding that patients with this variant have no GAA cross-reactive immunological material in protein isolated from skin fibroblast cultures i.e. CRIM-negative (PMID 22252923). The highest population minor allele frequency in gnomAD for this variant is 0.000008834 in the European non-Finnish population, meeting PM2 (<0.001). This variant has been reported in at least 15 patients who also meet the LSD VCEP's PP4 criterion (PMIDs 12923862, 16917947, 17056254, 18285536, 21484825, 22237443, 24158270, 26497565). The c.2237G>A variant was found in compound heterozygosity with c.-32-13T>G in 9 of 40 Italian patients studied; six of these patients meet PP4 and in 4 of those patients the phase was confirmed in trans (PMID 16917947) (4.5 points). Additional patients meeting PP4 have been reported to be compound heterozygous for the variant and c.-32-13T>G, c.2481+110_2646+39del, c.1128_1129delinsC, c.670C>T (p.Arg224Trp), c.853C>T (p.Pro285Ser) (PMIDs 12923862, 17056254, 18285536, 21484825, 22237443); the phase was not confirmed in any of these cases. Four patients meeting PP4 criteria are reported to be homozygous for the variant (PMID 26497565). Four additional patients have been reported with this variant but residual GAA activity was not reported, and therefore PP4 cannot be assessed (PMID 18429042, 24269976). Based on this data, PP4 and PM3_Very Strong are met. There is a ClinVar entry for this variant (Variation ID: 280063; 2 star review status) with 5 submitters all classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PM3_Very strong, PP4.

Met criteria codes

PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 for this variant is 0.00001 (European non-Finnish), meeting the ClinGen LSD VCEP's threshold for PM2 (<0.001).
PM3_Very Strong	✔	This variant has been reported in at least 15 patients who also meet the LSD VCEP's PP4 criterion (PMIDs 12923862, 16917947, 17056254, 18285536, 21484825, 22237443, 24158270, 26497565). The c.2237G>A variant was found in compound heterozygosity with c.-32-13T>G in 9 of 40 Italian patients studied; six of these patients meet PP4 and in 4 of those patients the phase was confirmed in trans (PMID 16917947) (4.5 points). Additional patients meeting PP4 have been reported to be compound heterozygous for the variant and c.-32-13T>G, c.2481+110_2646+39del, c.1128_1129delinsC, c.670C>T (p.Arg224Trp), c.853C>T (p.Pro285Ser) (PMID 12923862, 17056254, 18285536, 21484825, 22237443); the phase was not confirmed in any of these cases. Four patients meeting PP4 criteria are reported to be homozygous for the variant (PMID 26497565). Four additional patients have been reported with this variant but residual GAA activity was not reported, and therefore PP4 cannot be assessed (PMID 18429042, 24269976). Based on this data, PM3_Very Strong is met.

PubMed:12923862

Seven patients are compound heterozygous for c.2237G>A (p.Trp746Ter) and c.-32-13T>G, a well-known pathogenic variant. The variants are confirmed to be in trans. Five out of the seven patients meet PP4 criteria. 5 points were awarded. PubMed:16917947

Patient 1 is compound heterozygous for c.2237G>A (p.Trp746Ter) and c.1753G>A (p.Glu579Lys) and patient 9 is compound heterozygous for c.2237G>A (p.Trp746Ter) and c.378G>A (p.Trp126Ter). The phase of the variants was not confirmed. These patients do not meet PP4 criteria and therefore no points were awarded. PubMed:24269976

Patient 1 is compound heterozygous for c.2237G>A (p.Trp746Ter) and c.853C>T (p.Pro285Ser). c.853C>T (p.Pro285Ser) is likely pathogenic based on assessment by the ClinGen VCEp. The phase of the variants was not confirmed. This patient meets PP4 criteria. However, c.2237G>A (p.Trp746Ter) was used to calculate PM3 strength for c.853C>T (p.Pro285Ser) so PM3 was not used here to avoid a circular dependency. PubMed:21484825

Three patients are compound heterozygous for c.2237G>A (p.Trp746Ter) and c.-32-13T>G, a well-known pathogenic variant. The phase of the variants was not confirmed. One out of the threee patients meet PP4 criteria. No points were awarded since the phase was not confirmed and in trans data for c.-32-13T>G has already been counted. PubMed:24158270

PubMed:26497565

Patient 4 is compound heterozygous for c.2237G>A (p.Trp746Ter) and c.525delT (p.Glu176fsX45) and patient 11 is compound heterozygous for c.2237G>A and c.1655T>C (p.Leu552Pro). These patients do not meet PP4 criteria and therefore no points were awarded. PubMed:18429042

Patient 2 is compound heterozygous for c.2237G>A (p.Trp746Ter) and c.1128_1129delinsC. c.1128_1129delinsC is pathogenic based on assessment by the ClinGen LSD VCEP. The phase of the variants was not confirmed. This patient meets PP4 criteria. However, c.2237G>A (p.Trp746Ter) was used to calculate PM3 strength for c.1128_1129delinsC so PM3 was not used here to avoid a circular dependency. PubMed:22237443

Patient 13 is compound heterozygous for c.2237G>A (p.Trp746Ter) and c.-32-13T>G, a well-known pathogenic variant. The phase of the variants was not confirmed. This patient meets PP4 criteria. No points were awarded since the phase was not confirmed and in trans data for c.-32-13T>G has already been counted. PubMed:17056254

PVS1	✔	This variant is predicted to result in a premature stop codon that is detected by nonsense mediated decay resulting in lack of gene product.
PP4	✔	This variant has been reported in at least 15 patients with either <10% normal GAA activity in lymphocytes, leukocytes or muscle samples, or <30% normal in cultured fibroblasts, or in the affected range in a clinically validated dried blood spot assay (PMIDs 12923862, 16917947, 17056254, 18285536, 21484825, 22237443, 24158270, 26497565). This meets the criteria for PP4.

Patient 3 has GAA enzyme activity of 0.46 nmol/mg/hr (normal 21.4 +/- 6.2 nmol/mg/hr). PubMed:12923862
Patient 8 has 4.3% normal GAA activity in lymphocytes, patient 11 has 10% normal GAA activity in muscle, patient 13 has no GAA activity (unspecified tissue), patient 18 has 10% normal GAA activity in lymphocytes, patient 19 has 8% normal GAA activity in lymphocytes, patient 29 has 3.7% normal GAA activity in muscle, and patient 35 has 0.02% normal GAA activity in muscle. PubMed:16917947
Patient 1 has fibroblast GAA activity of 0.1-1.0% normal. PubMed:21484825
Patient 19 has 2.1% normal GAA activity in muscle tissue. PubMed:24158270
Patient 2 has no GAA activity (tissue not specified). PubMed:22237443
Patient 13 has GAA enzyme activity of 0.01 nmol/min/mg protein in lymphocytes (normal 0.17-0.42). PubMed:17056254

Curation History

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